

Antihyperlipidemic Drugs



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Hyperlipidemia =  Plasma Cholesterol (>200 mg/dL) and/or  Plasma Triglycerides (>150 mg/dL)

Hypercholesterolemia *Hypertriglyceridemia*

Hyperlipidemia  Atherosclerosis

- *coronary heart disease*
- *Stroke*

Hyperlipidemia

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graph TD; A[Hyperlipidemia] --> B[Primary genetic defects]; A --> C[Secondary]; C --> C1[• Drug-induced (e.g., GC, beta-blockers, diuretics)]; C --> C2[• Disease-induced (e.g., DM, CRF, HypoThyr)]; C --> C3[• Dietary habits!!];
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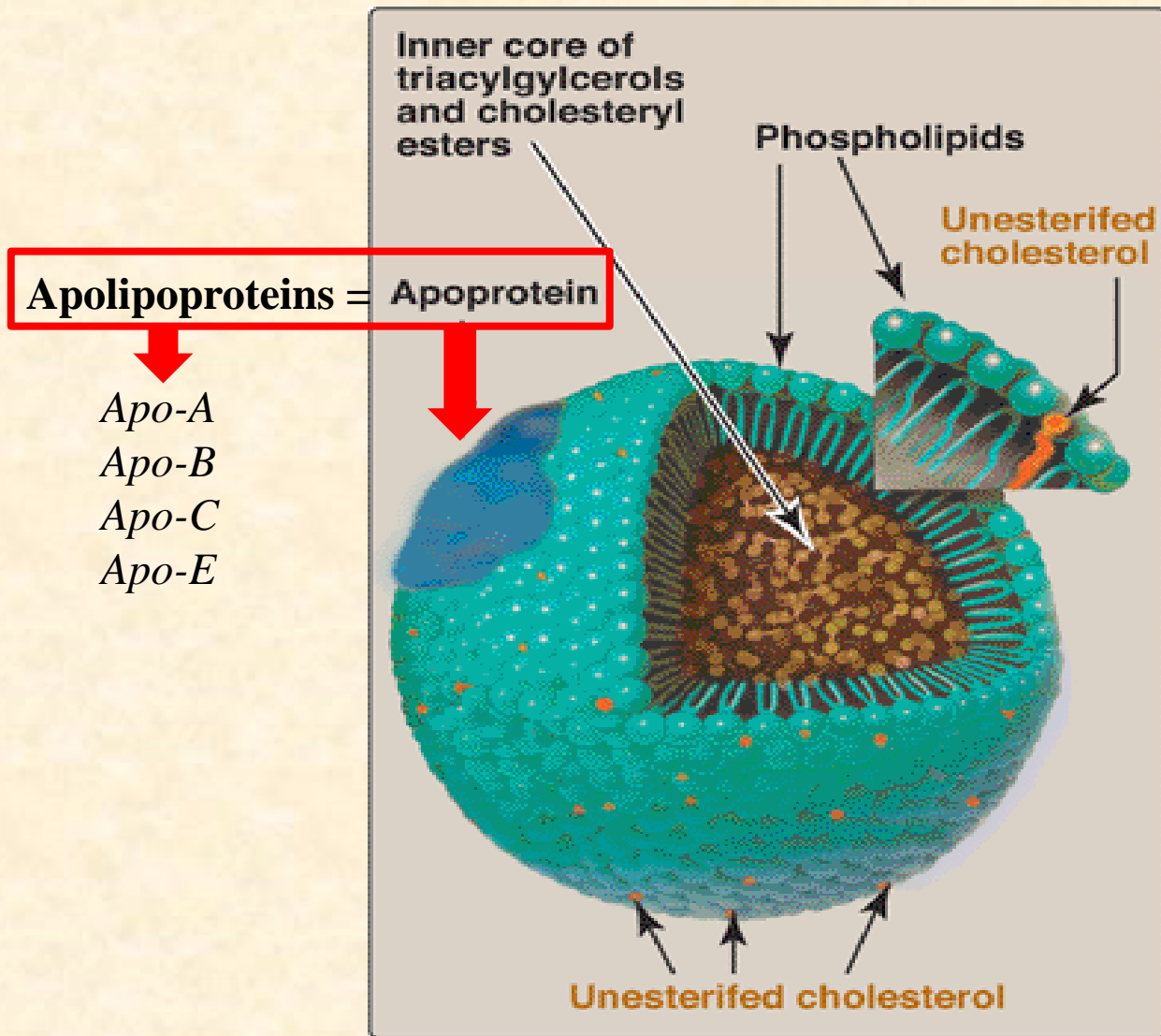
Primary

genetic defects

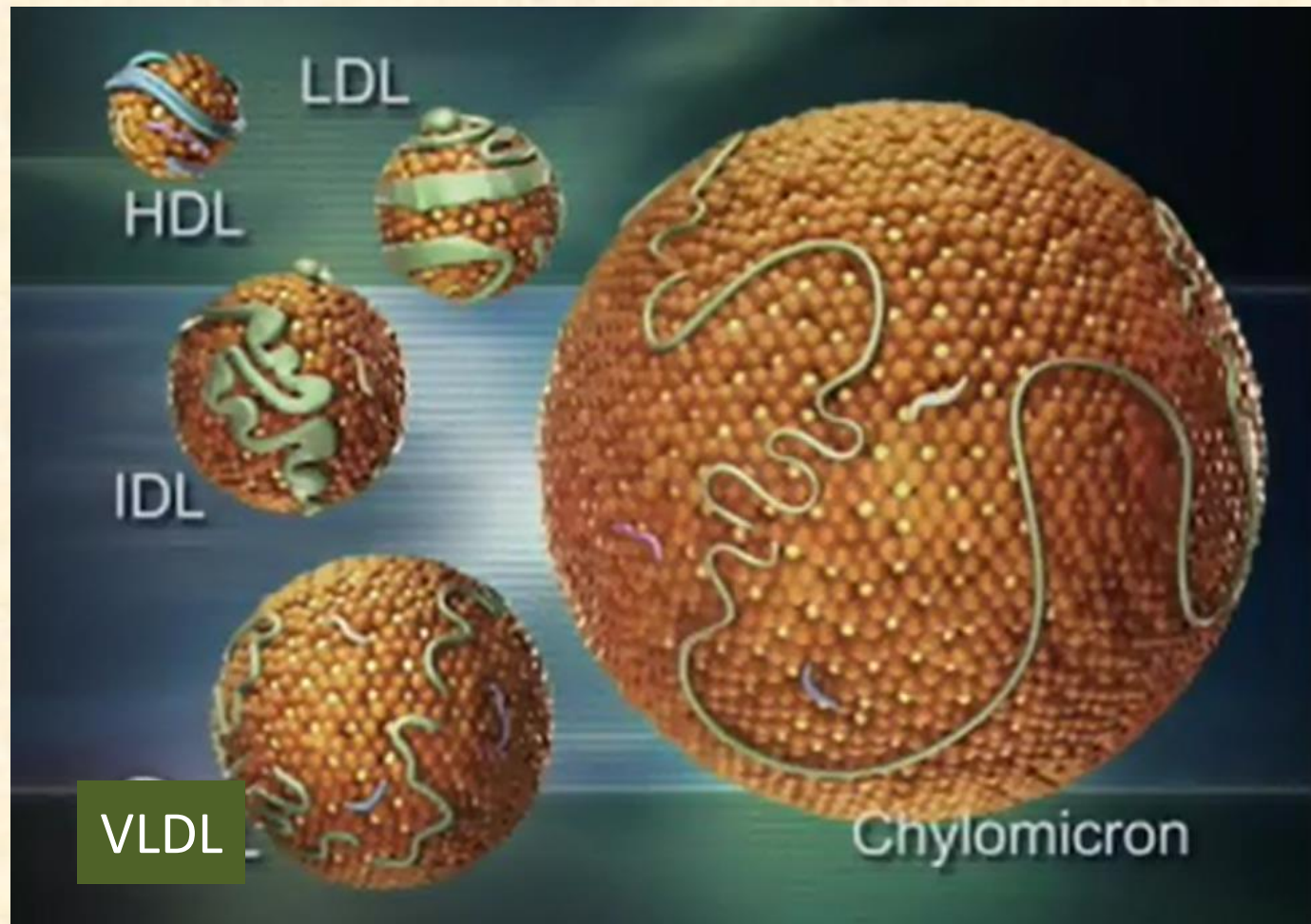
Secondary

- Drug-induced (*e.g., GC, beta-blockers, diuretics*)
- Disease-induced (*e.g., DM, CRF, HypoThyr*)
- Dietary habits!!

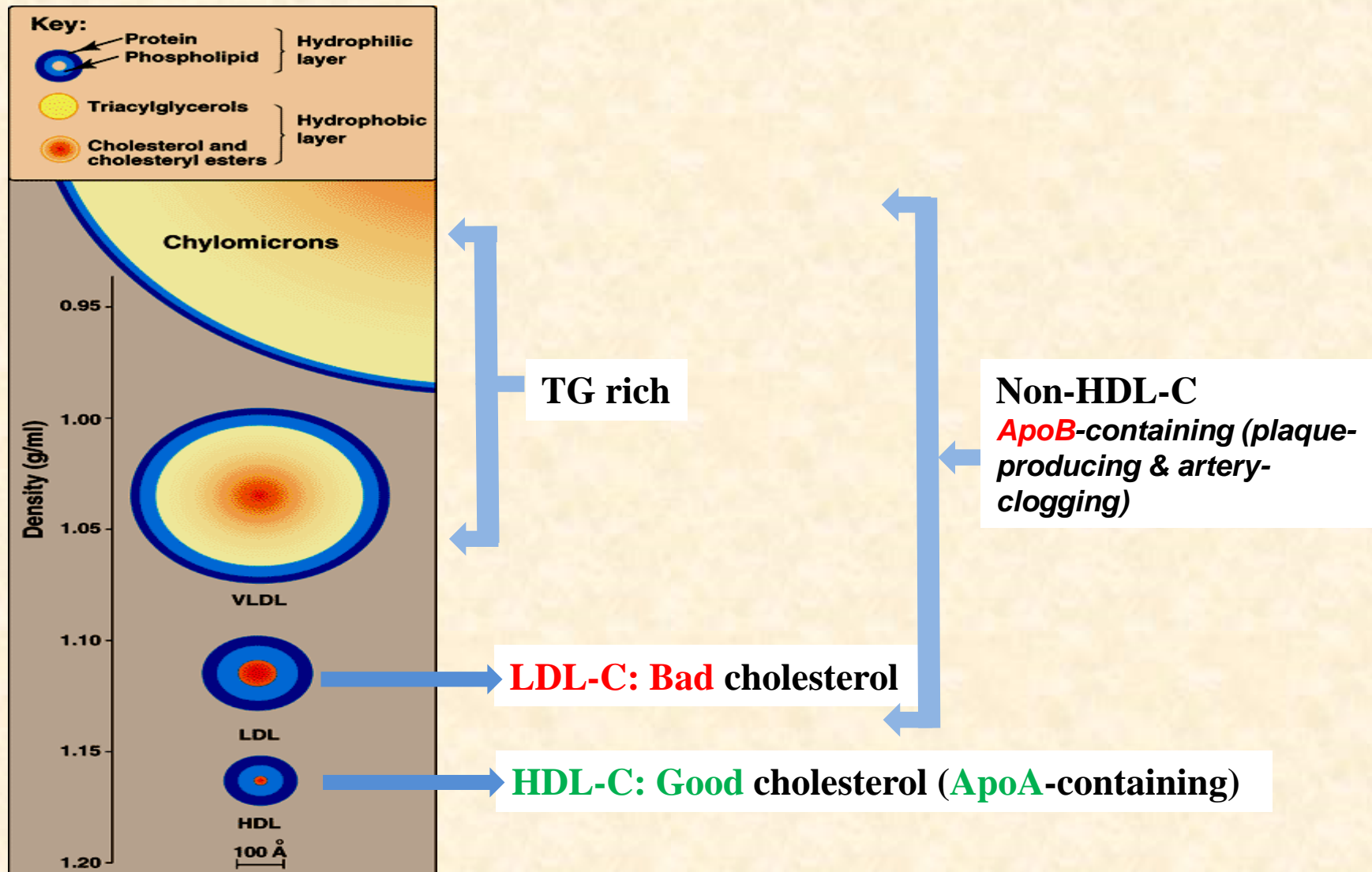
Structure of a typical lipoprotein particle

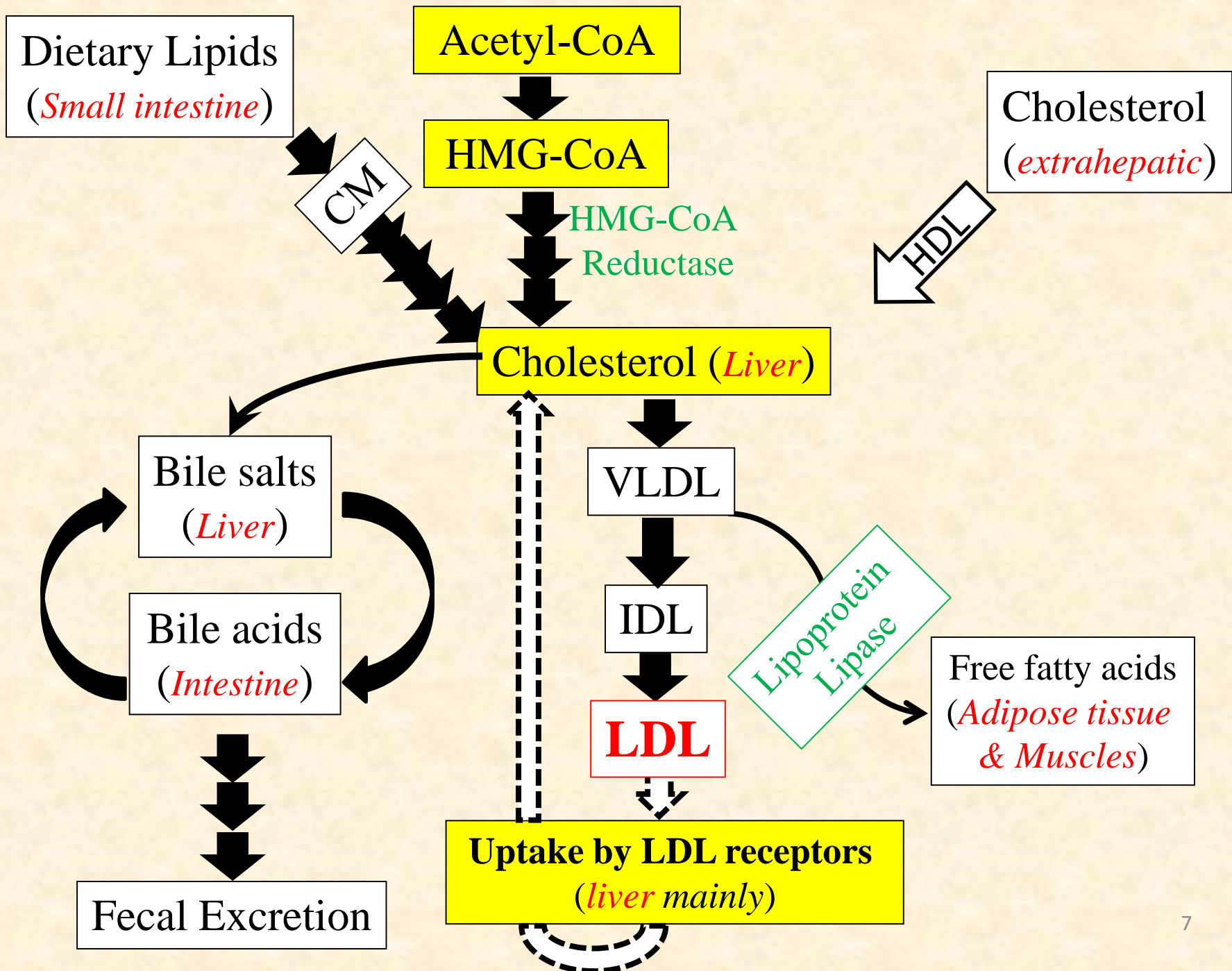


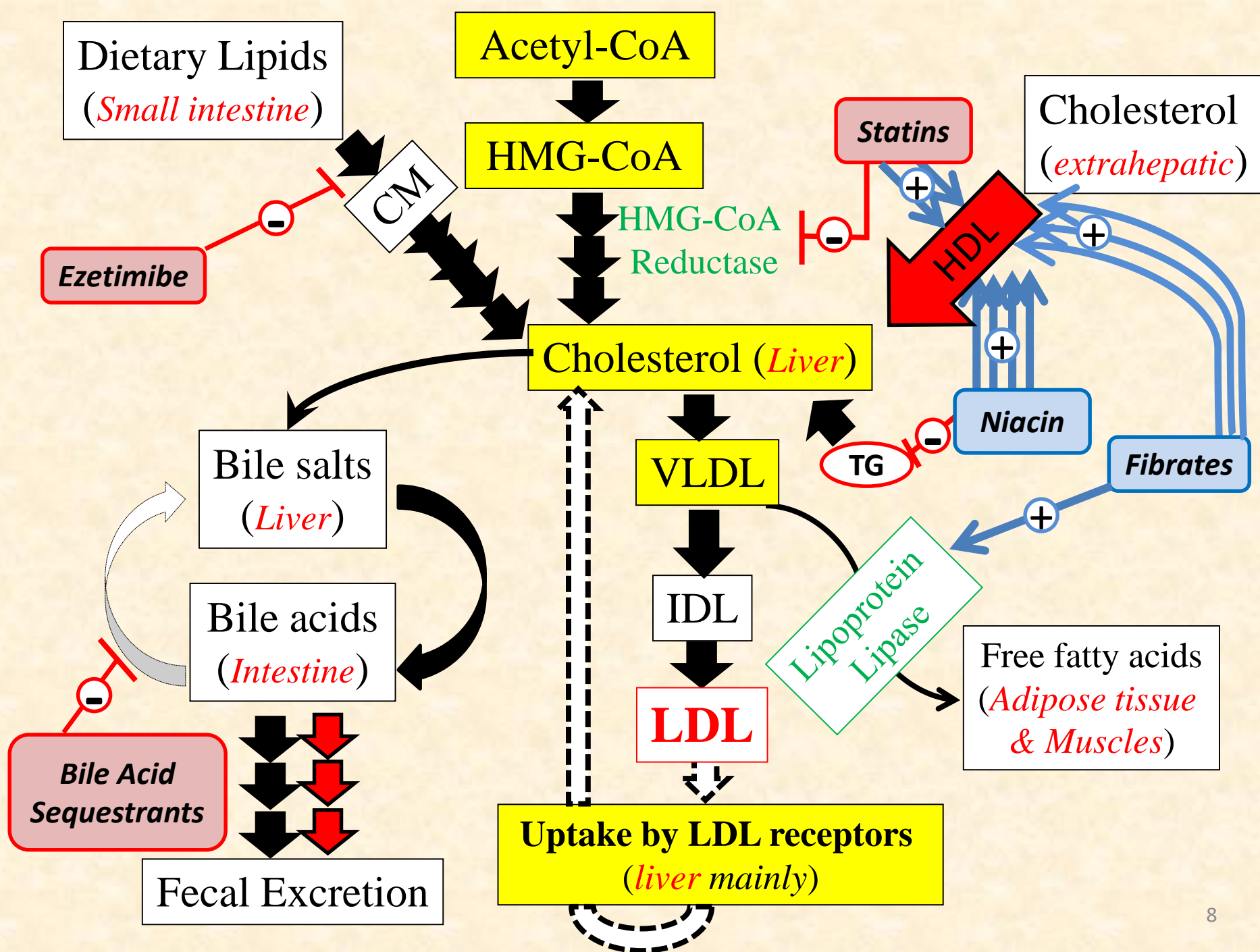
Size and density of Serum lipoproteins



Size and density of Serum lipoproteins

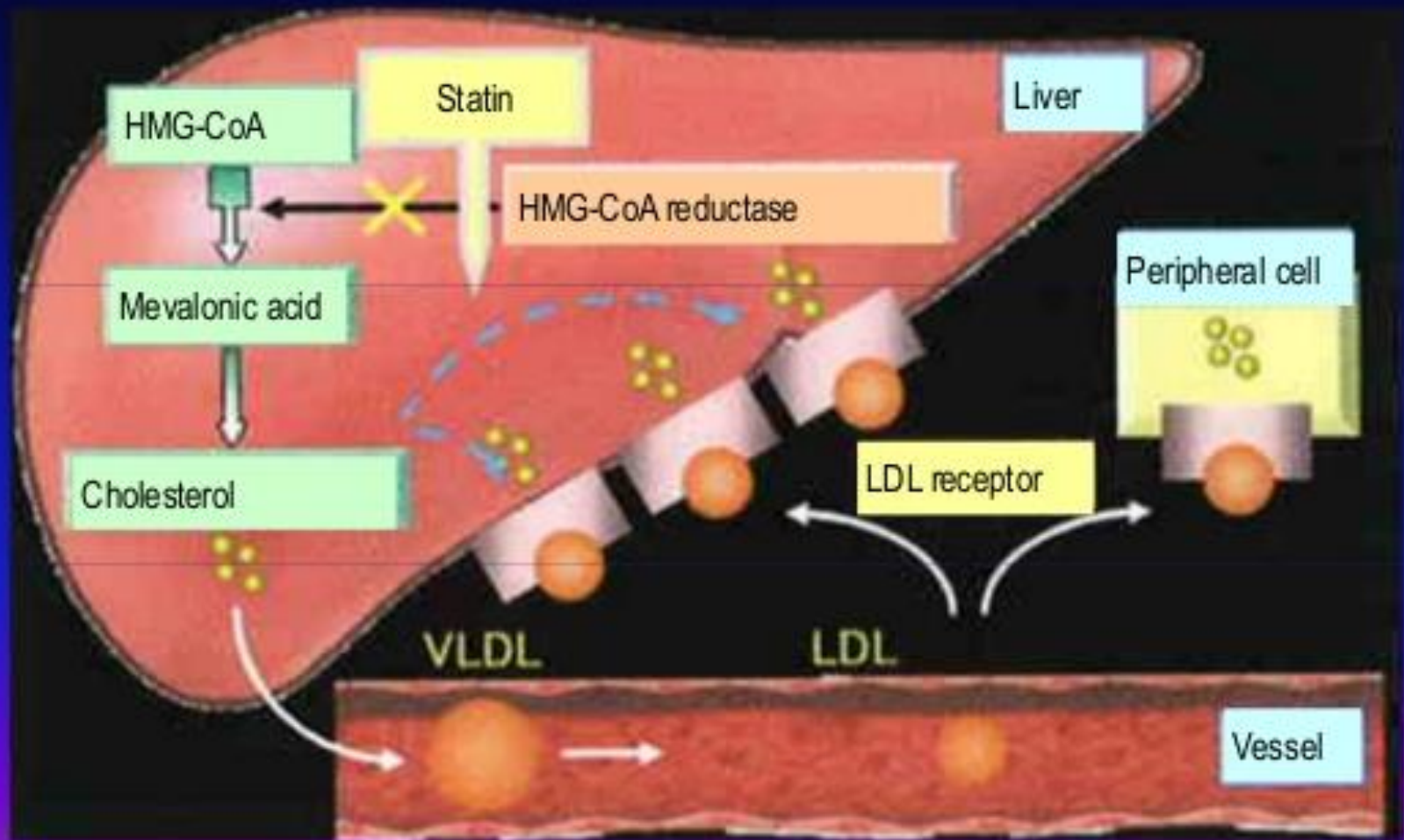




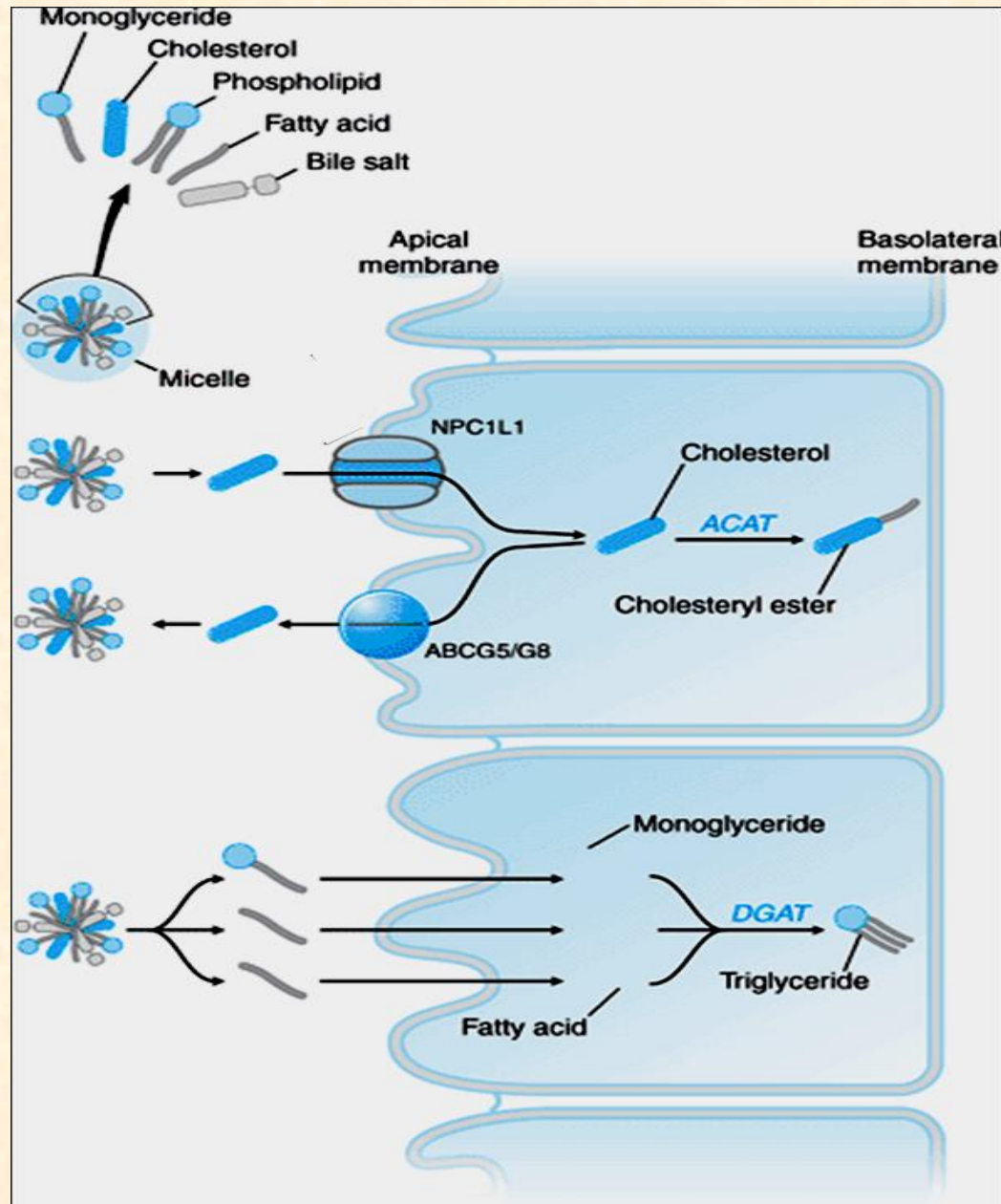


	Statins <i>e.g., simvastatin</i> <i>pravastatin</i> <i>Fluvastatin</i> <i>Atorvastatin</i> <i>rosuvastatin</i>	Bile Acid Sequestrants <i>e.g.,</i> <i>cholestyramine</i> <i>colestipol</i> <i>colesevelam</i>	Cholesterol Absorption Inhibitor <i>Ezetimibe</i>	Fibrates <i>e.g.,</i> <i>gemfibrozil</i> <i>fenofibrate</i>	Niacin (Nicotinic acid, Vit.B3)
M.O.A	1) \ominus HMG-CoA Reductase <i>(competitive)</i> $\rightarrow\rightarrow\rightarrow$ $\uparrow\uparrow$ LDL receptors expression \rightarrow \downarrow LDL cholest. 2) \uparrow HDL synthesis (\uparrow ApoAI)	Bind non-covalently to bile acids \rightarrow non-absorbable complex \rightarrow fecal excr.	\ominus NPC1L1 transport channel \rightarrow \downarrow cholest. absorpt.	1) PPAR α agonists \rightarrow \uparrow Lipoprotein lipase synthesis & activity (\downarrow ApoCIII) \rightarrow \downarrow plasma VLDL 2) \uparrow HDL synthesis (\uparrow ApoAI)	1) \ominus adipose tissue lipase \rightarrow \downarrow plasma FFA \rightarrow \ominus hepatic VLDL synth. 2) \uparrow HDL half-life (\downarrow ApoAI clearance)

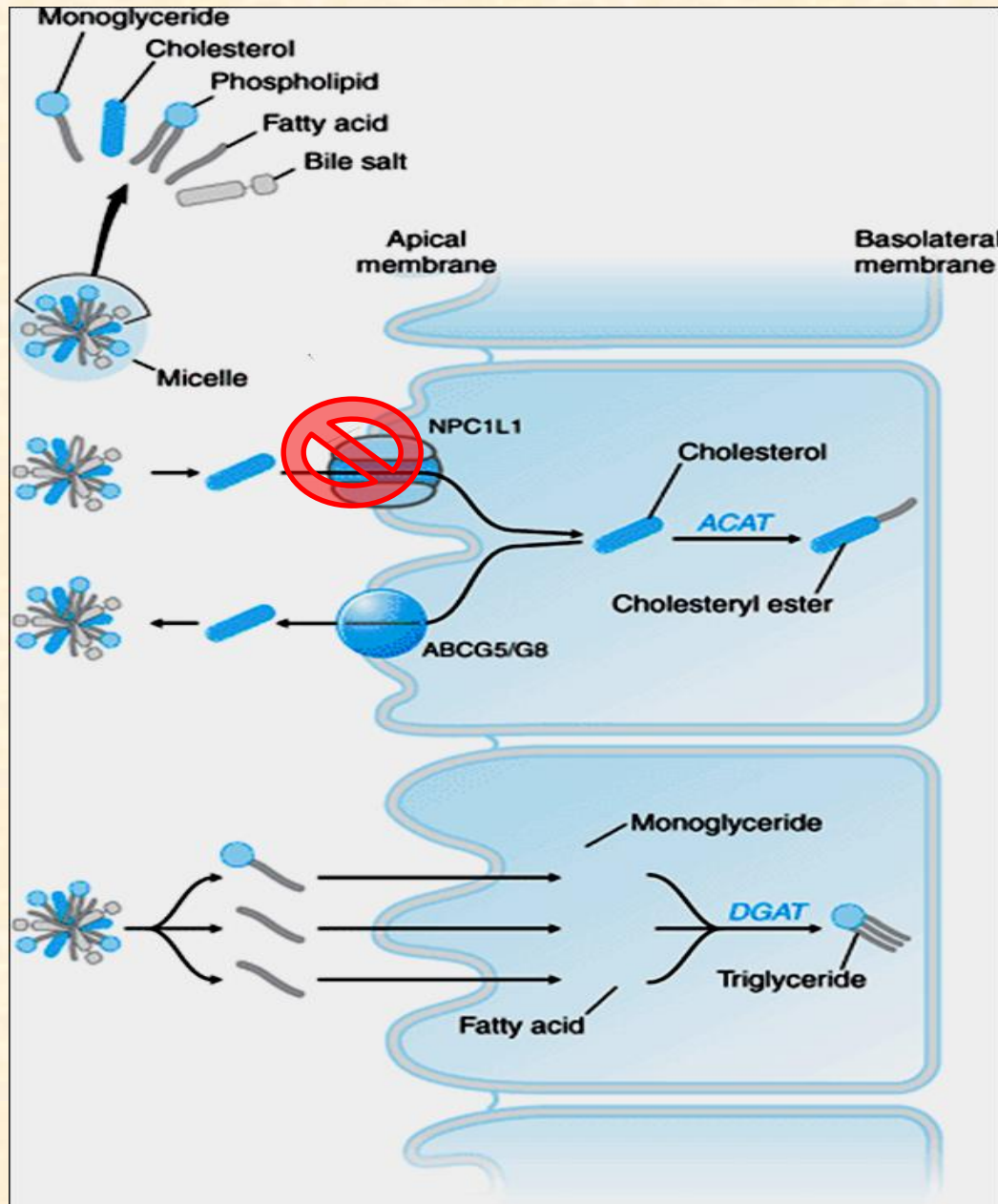
Statin Mechanism Of Action



Absorption of cholesterol and triglycerides



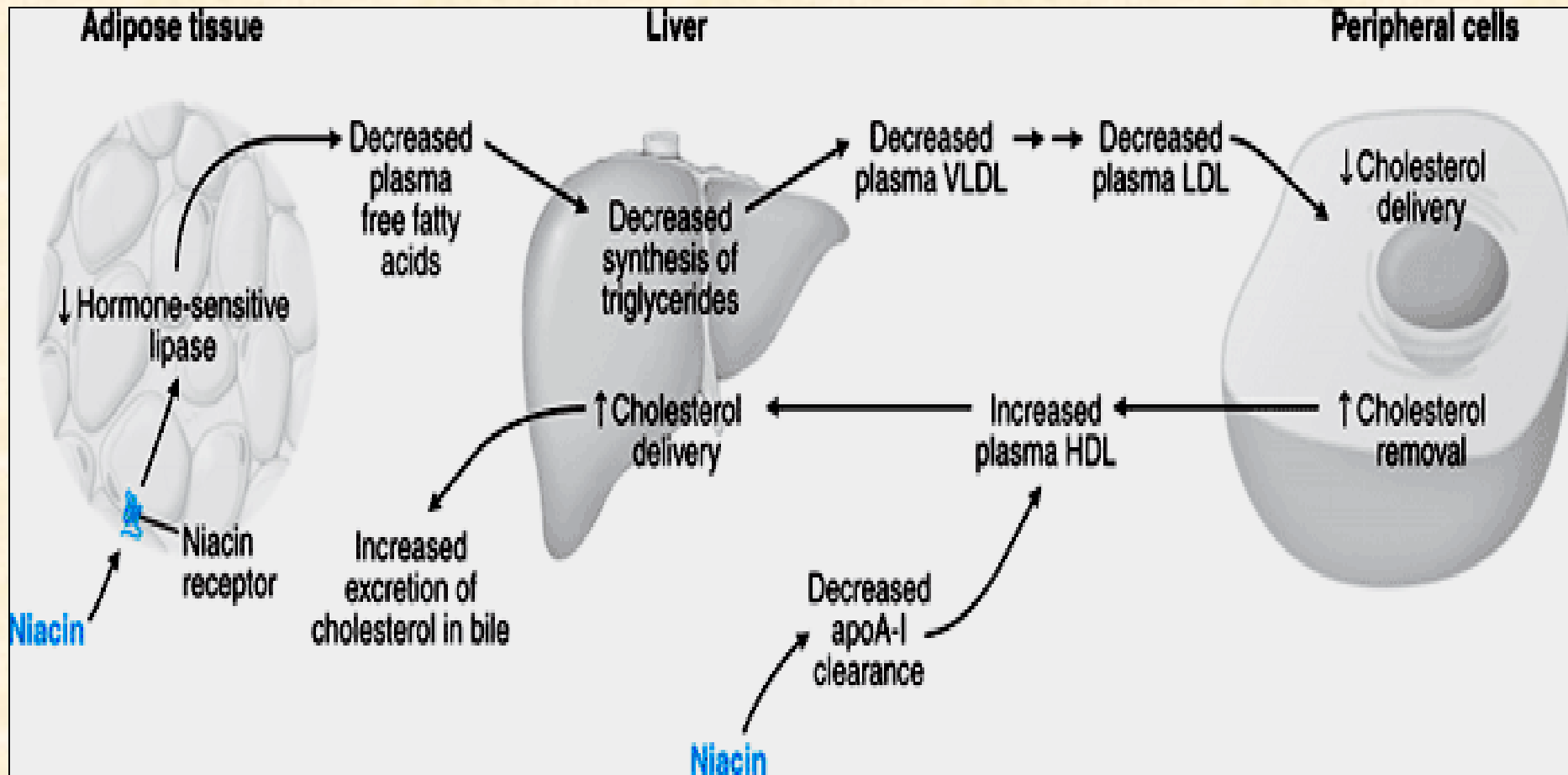
Mechanism of Action of Ezetimibe


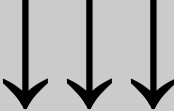


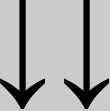
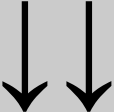

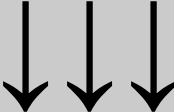





■ Fibrates : Mechanism of action



Niacin Mechanisms of action



	Statins <i>e.g., simvastatin, pravastatin, Fluvastatin atorvastatin, rosuvastatin</i>	Bile Acid Sequestrants <i>e.g., cholestyramine, colesevelam, colestipol</i>	Cholesterol Absorption Inhibitor <i>Ezetimibe</i>	Fibrates <i>e.g., gemfibrozil, fenofibrate</i>	Niacin (Nicotinic acid, Vit.B3)
LDL-C					
TG					
HDL-C					

Rhabdo

- **Striated**

Myo

- **Muscle**

Lysis

- **Breakdown**

*This is urine
from a patient
with
Rhabdomyolysis*



Gemfibrozil
+
some Statin drugs

	Statins <i>e.g., simvastatin, pravastatin, Fluvastatin atorvastatin, rosuvastatin</i>	Bile Acid Sequestrants <i>e.g., cholestyramine , colesevelam, colestipol</i>	Cholesterol Absorption Inhibitor <i>Ezetimibe</i>	Fibrates <i>e.g., gemfibrozil, fenofibrate</i>	Niacin (Nicotinic acid, Vit.B3)
D.I.	1) Gemfibrozil → Rhabdomyolysis. 2) Warfarin → ↑ anti-coagulant activity (<i>Cyp3A4 inhib.</i>). 3) CYP450 inhibitors → ↑ statin levels	↓ absorption of concurrently administered drugs		1) Warfarin → ↑ anti-coagulant activity (<i>Cyp3A4 inhib.</i>). 2) CYP450 inhibitors → ↑ fibrates levels	

	Statins <i>e.g., simvastatin</i> <i>pravastatin</i> <i>Fluvastatin</i> <i>Atorvastatin</i> <i>rosuvastatin</i>	Bile Acid Sequestrants <i>e.g.,</i> <i>cholestyramine</i> <i>colestipol</i> <i>colesevelam</i>	Cholesterol Absorption Inhibitor <i>Ezetimibe</i>	Fibrates <i>e.g.,</i> <i>gemfibrozil</i> <i>fenofibrate</i>	Niacin (Nicotinic acid, Vit.B3)
PK	pravastatin & rosuvastatin are <u>NOT</u> metabolized by CYP450	<ul style="list-style-type: none"> ▪Non-absorbable ▪Administered after meals 	Enterohep. circulation	<ul style="list-style-type: none"> ▪Metab. by CYP450 ▪Inhibit Cyp3A4 	

	Statins <i>e.g., simvastatin</i> <i>pravastatin</i> <i>Fluvastatin</i> <i>Atorvastatin</i> <i>rosuvastatin</i>	Bile Acid Sequestrants <i>e.g.,</i> <i>cholestyramine</i> <i>colestipol</i> <i>colesevelam</i>	Cholesterol Absorption Inhibitor <i>Ezetimibe</i>	Fibrates <i>e.g.,</i> <i>gemfibrozil</i> <i>fenofibrate</i>	Niacin (Nicotinic acid, Vit.B3)
S.E.	<ul style="list-style-type: none"> ▪ GI discomfort ▪ ↑ALT&AST. ▪ Myositis (myopathy) ▪ Myalgia 	<ul style="list-style-type: none"> ▪ Abdominal bloating. ▪ ↓Absorpt. of fat-soluble vitamins 	GI discomfort	<ul style="list-style-type: none"> ▪ GI discomfort. ▪ Cholesterol Gallstones. 	<ul style="list-style-type: none"> ▪ PG-mediated skin flushing & pruritis (<i>tachyphylaxis</i>). ▪ Hyperuricemia (?) ▪ Hyperglycemia (?) ▪ GI discomfort.
Contra-indic.	<ul style="list-style-type: none"> ▪ Pregnancy, lactation ▪ Childhood 		Hepatic insufficiency		<ul style="list-style-type: none"> ▪ Arthritis ▪ T2DM ▪ Active peptic ulcer

For the following questions, write the appropriate answer as a SINGLE word or as A FEW words in the following allocated spaces ONLY.

IMPORTANT: Questions that request drug names to be written, mention ONLY ONE drug name for each allocated space.

- 1) The following 3 statins are metabolized by CYP450: A) *simvastatin*
B) *Fluvastatin* And C) *Atorvastatin*
- 2) **Niacin** is an antihyperlipidemic agent which is contraindicated in patients with gouty arthritis.
- 3) The following category of antihyperlipidemics is the most efficacious in suppressing hypertriglyceridemia: **Fibrates**
- 4) The molecular target which is inhibited by ezetimibe is **NPC1L1**